EXHIBIT D

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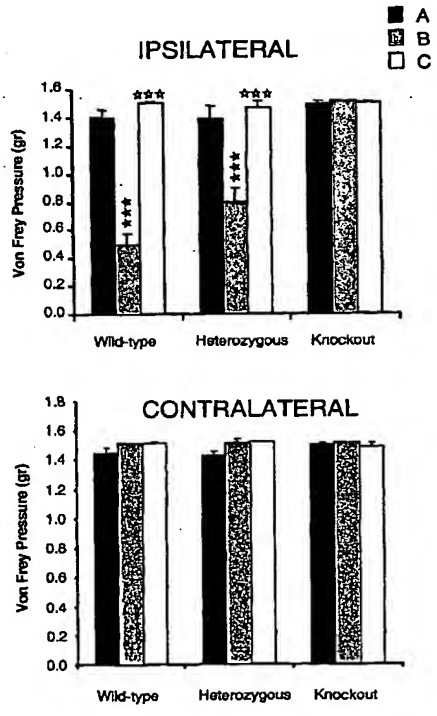
[Continued on next page]

(54) Title: USE OF COMPOUNDS ACTIVE ON THE SIGMA RECEPTOR FOR THE TREATMENT OF MECHANICAL ALLODYNIA

(57) Abstract: The present invention refert to the use of compounds active on the sigma receptor for the treatment of mechanical allodynia.



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Declaration under Rule 4.17:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Use of compounds active on the sigma receptor for the treatment of mechanical allodynia

Field of the Invention

The present invention refers to the use of compounds active on the sigma receptor for the treatment of the symptoms of mechanical allodynia, as well as treatment of the disease causing the symptoms, the prevention or the prophylaxis of the symptoms of mechanic allodynia, as well as the prevention or the prophylaxis of the disease causing the symptoms.

Background of the Invention

The treatment of pain conditions is of great importance in medicine. There is currently a world-wide need for additional pain therapy. The pressing requirement for a specific treatment of pain conditions or as well a treatment of specific pain conditions which is right for the patient, which is to be understood as the successful and satisfactory treatment of pain for the patients, is documented in the large number of scientific works which have recently and over the years appeared in the field of applied analgesics or on basic research on nociception.

PAIN is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). Even though pain is always subjective its causes or syndromes can be classified.

Especially mechanical allodynia which in the past years has developed into a major health problem in broad areas of the population needs a very specific treatment, especially considering that any treatment of mechanical allodynia is extremely sensitive to the causes behind the pain, be it the disease ultimately causing it or the mechanistic pathway over which it develops.

Therefore, it was the underlying problem solved by this invention to find new ways of treating mechanical allodynia.

So, the main object of this invention is the use of a compound binding to the sigma receptor in the production of a medicament for the treatment of mechanical allodynia.

This/these compound/s may be in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.

While working on compounds binding to the sigma receptor and with models like knock-out mice it was surprisingly found out that mechanical allodynia is connected to the sigma receptor so that compounds binding to the sigma receptor were acting on mechanical allodynia with a high potency.

"Treating" or "treatment" as used in this application are defined as including the treatment of the symptoms - of mechanical allodynia - as well as treatment of the disease or disease consequences causing the symptoms, the prevention or the prophylaxis of the symptoms - of mechanical allodynia - as well as the prevention or the prophylaxis of the disease or disease consequences causing the symptoms. Preferably "treating" or "treatment" as used in this application are defined as including the treatment of the symptoms - of mechanical allodynia - as well as treatment of the disease consequences causing the symptoms, the prevention or the prophylaxis of the symptoms - of mechanical allodynia - as well as the prevention or the prophylaxis of the disease consequences causing the symptoms. Most preferably "treating" or "treatment" as used in this application are defined as including the treatment of the symptoms of mechanical allodynia, and the prevention or the prophylaxis of the symptoms of mechanical allodynia.

"The sigma receptor/s" as used in this application is/are well known and defined using the following citation: This binding site represents a typical protein different from opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish at least two subtypes of σ receptors (R. Quiron et al., Trends Pharmacol. Sci. 13, 85-86 (1992); M.L.Leitner, Eur. J. Pharmacol. 259, 65-69 (1994); S.B. Hellewell and W.D. Bowen; Brain Res. 527, 244-253 (1990)) (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). The protein sequence of sigma receptors (Sigma 1 (σ1) and Sigma 2 (σ2)) is known (e.g. Prasad, P.D. et al., J. Neurochem. 70 (2), 443-451 (1998)) and they show a very high affinity for e.g. pentazocine.

"Compound/s binding to the sigma receptor" or "sigma ligand" as used in this application is/are defined as having an IC_{50} value of ≤5000 nM, more preferably ≤ 1000 nM, more preferably ≤500 nM. More preferably, the IC_{50} value is ≤250 nM. More preferably, the IC_{50} value is ≤100 nM. Most preferably, the IC_{50} value is ≤ 50 nM. Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least ≥50% displacement using 10 mM radioligand specific for the sigma receptor (e.g. preferably ^{1}H-pentazocine) whereby the sigma recepor may be any sigma receptor subtype. Preferably, said compounds bind to the sigma-1 receptor subtype.

Compounds binding to the sigma receptor generally also known as sigma ligands are well known in the art with many of them falling under the definition for "Compound/s binding to the sigma receptor" set up above. Still even though there are many uses known for sigma ligands such as antipsychotic drugs, anxiolytics, antidepressants, the treatment of stroke, antiepileptic drugs and many other indications including anti-migraine and general pain (mostly analgesia) there is nowhere any mentioning of these compounds being useful against mechanical allodynia.

Preferably, compounds selected from the group consisting of amitriptyline, desipramine, fluoxetine, methadone and tiagabine, are disclaimed from the present invention. These compounds have been shown to bind to the sigma receptor and have an IC_{50} value ≥100 nM.

Preferably, compounds selected from the group consisting of agmatine, alfentanil, all-trans retinoic acid (ATRA), Erythropoietin, Etanercept, GV196771, GV196771A, GW406381X, KRN5500, L-N (6)-(1-iminoethyl) lysine (L-NIL), LY379268, LY389795, neurotropin, N-methyl-D-aspartic acid, peptide analog of thymulin (PAT), Propentofylline, ReN-1869 [(R)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1- propyl)-3-piperidine carboxylic acid], R-phenylisopropyl-adenosine (R-PIA), SD-282, Semaphorin3A, SHU9119, T62 (2-amino-3-(4-chlorobenzoyl)-5,6,7,8-tetrahydrobenzothiophene) and ziconotide are disclaimed from the present invention. The majority of these compounds has an IC_{50} ≥100 nM with respect to binding the sigma receptor.

Compounds binding to the sigma receptor known in the art and matching the criteria of sigma ligand (i.e. having an IC_{50} ≤ 5000 nM) as mentioned above, are listed below. Some of these compounds may bind to the sigma-1 and/or the sigma-2 receptor. Preferably, these compounds are in form of a salt, a base or an acid. Also preferably, the salts/bases/acids indicated in the list are to be understood as being exemplary and therefore may respresent any salt, base or acid of the compound.

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)-Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-Yl]-Methanone	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)

1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-{[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl}-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2- Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-Ylmethyl Ester	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino]Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline
ARC 239 DiHCl	Astemizole
Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063

Benextramine TetraHCl	Benfluorex HCl
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepridil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DiHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl
Buclizine HCl	Buflomedil HCl
Bupropion HCl	Buspirone HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 723C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DiHCl DiH2O
Carvedilol	Cephapirin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate
Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl
Clidinium Bromide	Clobenpropit 2HBr
Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphemanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl
Donepezil HCl	Doxepin HCl

Droperidol	Duloxetine
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Ethaverine HCl	Ethopropazine HCl
Eticlopride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate
Guanabenz Acetate	Guanadrel Sulfate
Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl
Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl
lomerizine diHCl	Loperamide HCl
Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl

N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-Piperazin-1-Yl}-Ethoxy)-Ethyl Ester
Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A
Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt
Perospirone	Perphenazine
Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenosafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino-Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Propericyazine	Propiomazine
Propranolol HCl	Protokylol
Protriptyline HCl	Pyrilamine Maleate
Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Rimantadine HCl
Risperidone	Ritanserin

Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296
Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Terconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate
Thioperamide Maleate	Thioproperazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-
Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Triprolidine HCl	Triprolidine HCl Z Isomer
Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

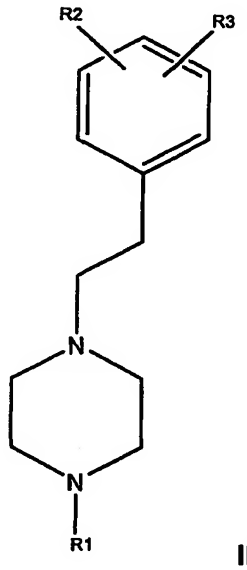
Another aspect of the present invention relates to BD-1063 and its derivatives, a compound binding to the sigma receptor, and its use for the production of a medicament for the treatment of mechanical allodynia.

The synthesis of BD-1063 and compounds structurally related (mostly those covered under formula IB) is described in detail in de Costa et al. (1993), J. Med. Chem. 36(16): 2311-2320 (referred to as compound 4 in Scheme I; p. 2312)

included here by reference. Accordingly the synthesis of the compound whose use is claimed in this invention is known and the compound thus is available to those skilled in the art, starting from the given information working analogously if necessary.

Compounds according to general formula IB have been shown to be sigma ligands according to the above mentioned definition.

Therefore, another aspect of the present invention is the use of a compound of general formula IB



IB

wherein

R1 is selected from C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

R2 and R3 are independently of each other selected from H; C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen, O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

in the production of a drug to treat mechanical allodynia.

In a preferred embodiment of the invention the compound used is a compound according to general formula IB, wherein R1 is selected from C_{1-6}-Alkyl, saturated or unsaturated, branched or not branched, unsubstituted or substituted with F, Cl, Br, I, NH_2, SH or OH.

In a preferred embodiment of the invention the compound used is a compound according to general formula IB, wherein R2 and R3 are independently of each other selected from H; C_{1-6}-Alkyl, saturated or unsaturated, branched or not branched, unsubstituted or substituted with F, Cl, Br, I, NH_2, SH or OH; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, branched or not branched, unsubstituted or substituted with F, Cl, Br, I, NH_2, SH or OH.

In a preferred embodiment of the invention the compound used is a compound according to general formula IB, wherein

R^1 is selected from C_{1-4}-Alkyl, saturated or unsaturated, substituted or not substituted, and branched or not branched;

preferably R^1 is selected from C_{1-4}-Alkyl, saturated, substituted or not substituted, and branched or not branched;

more preferably R^1 is selected from C_{1-4}-Alkyl, saturated, not substituted, and branched or not branched; namely CH_3, C_2H_5, C_3H_7, C_4H_9.

In a preferred embodiment of the invention the compound used is a compound according to general formula IB, wherein

R^2 and R^3 are independently of each other selected from H; OH, SH, NH_2, C_{1-4}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or

not branched; F, Cl, Br, I; O-C_{1-4}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

preferably R^2 and R^3 are independently of each other selected from H; OH, NH_2, C_{1-4}-Alkyl, saturated, substituted or not substituted, and branched or not branched; F, Cl, Br, I; O-C_{1-4}-Alkyl, saturated, not substituted, and branched or not branched.

In a preferred embodiment of the invention the compound used is a compound according to general formula IB, wherein

R^2 and R^3 are independently of each other selected from H, OH, NH_2, CH_3, C_2H_5, C_3H_7, C_4H_9, CF_3, CHF_2, Cl, F, Br, I, O-CH_3, O-C_2H_5, O-C_3H_7, O-C_4H_9;

preferably R^2 and R^3 are independently of each other selected from H, F, Cl and CF_3.

Here it is also preferred if R^2 and R^3 are in 3' and 4' position on the phenyl ring.

In a highly preferred embodiment of the invention the compound according to general formula IB used is 1-(3,4-dichlorophenethyl)-4-methylpiperazine, optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable ratio; in the form described or in form of an acid or base or in form of a salt, especially a physiologically acceptable salt, or in form of a solvate, especially a hydrate.

Unless otherwise stated, the compound of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon or ^{15}N-enriched nitrogen are within the scope of this invention.

Another aspect of the present invention relates to BD-1047, a compound binding to the sigma receptor, and its use for the production of a medicament for the treatment of mechanical allodynia.

BD-1047 (N1-(3,4-dichlorophenethyl)-N1,N2,N2-trimethylethane-1,2-diamine/ N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)-ethylamine) is, like BD-1063, commercially available and also a popular tool compound as sigma receptor ligands (K_i = 0.9 nM for sigma-1). As according to US2003/0171347A1, BD-1047 shows no or only slight binding to a selection of other relevant receptors (page 7, table2 and page 8, table 3).
The synthesis of BD-1047 is described in detail in de Costa et al. (1992), J. Med Chem. 35, 38-47, as well as WO92/22279 A1 showing compounds related to CNS disorders, where BD-1047 is described as a truncated version (compound 10 in Scheme 2, p.17), included herein by reference.

Another aspect of the invention is the use of BD-1047 and/or at least one compound of general formula IB as defined above for the production of a medicament for the treatment of neuropathic pain.

In the context of the whole invention, alkyl and cycloalkyl radicals are understood as meaning saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons, which can be unsubstituted or mono- or polysubstituted. In these radicals, C_{1-2}-alkyl represents C1- or C2-alkyl, C_{1-3}-alkyl represents C1-, C2- or C3-alkyl, C_{1-4}-alkyl represents C1-, C2-, C3- or C4-alkyl, C_{1-5}-alkyl represents C1-, C2-, C3-, C4-, or C5-alkyl, C_{1-6}-alkyl represents C1-, C2-, C3-, C4-, C5- or C6-alkyl, C_{1-7}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C_{1-8}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C_{1-10}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C10-alkyl and C_{1-18}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. Furthermore, C_{3-4}-cycloalkyl represents C3- or C4-cycloalkyl, C_{3-5}-cycloalkyl represents C3-, C4- or C5-cycloalkyl, C_{3-6}-cycloalkyl represents C3-, C4-, C5- or C6-cycloalkyl, C_{3-7}-cycloalkyl represents C3-, C4-, C5-, C6- or C7-cycloalkyl, C_{3-8}-cycloalkyl represents C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C_{4-5}-

cycloalkyl represents C4- or C5-cycloalkyl, C_{4-6}-cycloalkyl represents C4-, C5- or C6-cycloalkyl, C_{4-7}-cycloalkyl represents C4-, C5-, C6- or C7-cycloalkyl, C_{5-6}-cycloalkyl represents C5- or C6-cycloalkyl and C_{5-7}-cycloalkyl represents C5-, C6- or C7-cycloalkyl. In respect of cycloalkyl, the term also includes saturated cycloalkyls in which one or 2 carbon atoms are replaced by a heteroatom, S, N or O. However, mono- or polyunsaturated, preferably monounsaturated, cycloalkyls without a heteroatom in the ring also in particular fall under the term cycloalkyl as long as the cycloalkyl is not an aromatic system. The alkyl and cycloalkyl radicals are preferably methyl, ethyl, vinyl (ethenyl), propyl, allyl (2-propenyl), 1-propinyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, and also adamantyl, (if substituted also CHF_2, CF_3 or CH_2OH) as well as pyrazolinone, oxopyrazolinone, [1,4]-dioxane or dioxolane.

In the context of the whole invention, in connection with alkyl and cycloalkyl - unless expressly defined otherwise - the term substituted in the context of this invention is understood as meaning replacement of at least one hydrogen radical by F, Cl, Br, I, NH_2, SH or OH, "polysubstituted" radicals being understood as meaning that the replacement takes effect both on different and on the same atoms several times with the same or different substituents, for example three times on the same C atom, as in the case of CF_3, or at different places, as in the case of -CH(OH)-CH=CH-$CHCl_2$. Particularly preferred substituents here are F, Cl and OH. In respect of cycloalkyl, the hydrogen radical can also be replaced by OC_{1-3}-alkyl or C_{1-3}-alkyl (in each case mono- or polysubstituted or unsubstituted), in particular methyl, ethyl, n-propyl, i-propyl, CF_3, methoxy or ethoxy.

In a preferred embodiment of the present invention, with respect to compounds of general formula IB, R1, R2 and/or R3 are at least optionally substituted with F, Cl, Br, I, NH_2, SH or OH.

Referring to the whole invention, the term $(CH_2)_{3-6}$ is to be understood as meaning -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-, $(CH_2)_{1-4}$ is to be understood as meaning -CH_2-, -CH_2-CH_2-, -CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-, $(CH_2)_{4-6}$ is to be understood as meaning -CH_2-CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-CH_2-, etc.

An aryl radical is understood in the whole invention as meaning ring systems with at least one aromatic ring but without heteroatoms even in only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H-fluorenyl or anthracenyl radicals, which can be unsubstituted or monosubstituted or polysubstituted.

Additionally, in the context of the whole invention, a heteroaryl radical is understood as meaning heterocyclic ring systems which have at least one unsaturated ring and can contain one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur and can also be mono- or polysubstituted. Examples which may be mentioned from the group of heteroaryls are furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline.

In addition, referring to the whole invention, in connection with aryl and heteroaryl, substituted is understood as meaning substitution of the aryl or heteroaryl by R, OR, a halogen, preferably F and/or Cl, a CF_3, a CN, an NO_2, an NRR, a C_{1-6}-alkyl (saturated), a C_{1-6}-alkoxy, a C_{3-6}-cycloalkoxy, a C_{3-6}-cycloalkyl or a C_{2-6}-alkylene.

The term "salt" is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions.

The term "physiologically acceptable salt" is understood in particular, in the context of this invention, as salt (as defined above) formed either with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals - or with at least one, preferably inorganic, cation which are physiologically tolerated - especially if used on humans and/or mammals. Examples of physiologically tolerated salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, hydrobromide, monohydrobromide, monohydrochloride or hydrochloride, methiodide, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, hippuric acid picric acid and/or aspartic acid. Examples of physiologically tolerated salts of particular bases are salts of alkali metals and alkaline earth metals and with NH_4.

The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

According to the IASP "allodynia" is defined as "a pain due to a stimulus which does not normally provoke pain" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). Even though the symptoms of allodynia are most likely associated as symptoms of neuropathic pain this is not necessarily the case so that there are symptoms of allodynia not connected to neuropathic pain though rendering mechanical allodynia in some areas broader then neuropathic pain.

Mechanical allodynia is a form of allodynia where mechanical stimuli cause the painful sensation in contrast to thermal allodynia where the painful sensation comes from a thermal stimulus (e.g. heat).

"Neuropathic pain" is defined by the IASP as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (IASP, Classification of chronic pain,

2nd Edition, IASP Press (2002), 210). For the purpose of this invention included under this heading or to be treated as synonymous is "Neurogenic Pain" which is defined by the IASP as "pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral or central nervous system".

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The IASP draws the following difference between "allodynia", "hyperalgesia" and "hyperpathia" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212):

Allodynia	Lowered threshold	Stimulus and response mode differ
Hyperalgesia	Increased response	Stimulus and response rate are the same
Hyperpathia	Raised threshold; Increased response	Stimulus and response rate may be the same or different

In another preferred embodiment of the use according to the invention the mechanical allodynia derived from central pain.

In another preferred embodiment of the use according to the invention the mechanical allodynia derived from peripheral pain.

In another preferred embodiment of the invention the mechanical allodynia is derived from neuropathic pain.

In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an antagonist.

In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an inverse agonist.

In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as a partial antagonist.

In another possible embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an agonist.

In another embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as a mixed agonist/antagonist, a partial agonist or a partial antagonist.

In another embodiment of the invention the sigma receptor to which the "compound binding to the sigma receptor" is binding to is the sigma-1 receptor. Under this embodiment "Compound/s binding to the sigma receptor" as used in this application is/are defined as having an IC50 value $\leq$5000 nM, more preferably $\leq$1000 nM, more preferably $\leq$ 500 nM. More preferably, the IC_{50} value is $\leq$ 250 nM. More preferably, the IC_{50} value is $\leq$100 nM. Most preferably, the IC_{50} value is $\leq$50 nM. Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least $\geq$50% displacement using 10 mM radioligand specific for the sigma receptor (e.g. preferably ^{1}H-pentazocine) whereby the sigma recepor may be any sigma receptor subtype.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of $\leq$1000 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of $\leq$500 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of $\leq$250 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of $\leq$100 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of $\leq$50 nM.

Most preferably, "compounds highly specific for the sigma receptor" are defined as being "Compound/s binding to the sigma receptor", as defined above, having an IC_{50} value of $\leq$100 nM.

In a highly preferred embodiment of the present invention, the compound binding to the sigma receptor as defined above, is binding to the sigma-1 receptor subtype.

In another possible aspect of the invention, the compound binding to the sigma receptor as defined above, may bind to the sigma-2 receptor subtype.

In human therapeutics, the dose administered can be quite low depending on the route of administration and is well known in the art because sigma compounds are known therapeutics.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

Any medicament according to the invention contains the active ingredient as well as optionally at least one auxiliary material and/or additive and/or optionally another active ingredient.

The auxiliary material and/or additive can be specifically selected from conserving agents, emulsifiers and/or carriers for parenteral application. The selection of these auxiliary materials and/or additives and of the amounts to be used depends upon how the pharmaceutical composition is to be applied. Examples include here especially parenteral like intravenous subcutaneous or intramuscular application formulations but which could also be used for other administration routes.

Routes of administration preferably include intramuscular injection, intraveneous injection, subcutaneous injection, sublingual, bucal, patch through skin, oral ingestion, implantable osmotic pump, collagen implants, aerosols or suppository.

Included in this invention are especially also methods of treatments of a patient or a mammal, including men, suffering from mechanical allodynia using compounds binding to the sigma receptor.

The examples and figures in the following section describing pharmacological trials are merely illustrative and the invention cannot be considered in any way as being restricted to these applications.

Examples

Example 1: Von Frey-Model

The von Frey model is a model for allodynia, stimulated mechanically (mechanical allodynia).

Interest of the model:

- The injection of capsaicin to experimental animals produces acute pain followed by allodynia
- The mechanisms involved in capsaicin-induced acute pain and allodynia are relatively well known (mainly activation of peripheral nociceptors and sensitization of spinal cord neurons, respectively)

Hypothesis

- Capsaicin-induced allodynia is due to the release in the spinal cord of several substances including excitatory aminoacids (EA). Since sigma ligands modulate the effect of EA they would also modulate capsaicin-induced allodynia

Figure 1) shows the test protocol for all tests with von Frey filaments. After habituation mice were according to Figure 1 first treated with the test-compound (or not in controls). Then capsaicin (1% DMSO) is injected into their paw resulting in developing pain in the effected paw. The effected paw is then treated with a mechanical stimulus and the latency time before the paw is withdrawn is measured.

Example 2: Effect of NE-100 in the von Frey-Model.

NE-100 is a well known compound with high affinity to the sigma receptor, more specifically a known specific inhibitor of Sigma 1 (J Med Chem 1999, 42(19): 3965). This pharmacological test showed the effect of NE-100 a specific sigma receptor inhibitor in the von-frey model described in example 1, a model of allodynia.

As shown in Figure 2a) there is a dose dependency of the treatment with NE-100 showing analgesia in capsaicin-induced allodynia.

As demonstrated in Figure 2b) the treatment with NE-100 is effective specifically in allodynia or mechanical allodynia and not general pain as shown by the different efficacy depending on the force of the von-Frey filaments with 0.5 g being typically in the range of allodynia and 4 g clearly being in the general pain field.

Further as shown in Figure 2c) there is clear evidence that the effect of the treatment with NE-100 is clearly connected to its sigma inhibitor activity, as PRE-084 is a well known sigma receptor agonist counteracting the effect of NE-100.

Example 3: Effect of antisense ODN against the sigma receptor in the von Frey-Model.

2 well known antisense Oligodesoxynucleotides (ODN) against the sigma 1 receptor (King et al. (1997) Eur J Pharmacol 331:R5-R6 and Ueda et al. (2001) J.Pharmacol.Exp.Ther. 298, 703-710) were synthesized and according to the protocol shown in figure 3a) given on 4 consecutive days i.c.v. followed by a wash-out period and von-Frey tests according to example 1.

As can be seen in Figure 3b) both antisense ODNs show a strong effect on day one after treatment with mismatches not having any significant effect. This effect is washed out after 7 days as can be expected from antisense ODN.

The effectiveness and dose dependency is demonstrated in Figure 3c). Mismatches do not have any significant effect.

Further as demonstrated in Figure 3d) the treatment with the two known antisense ODNs is effective specifically in allodynia or mechanical allodynia and not general pain as shown by the different efficacy depending on the force of the von-Frey

filaments with 0.5 g being typically in the range of allodynia and 4 g clearly being in the general pain field.

Example 4: Effect of the von Frey-Model on KO mice.

KO mice lacking the sigma 1 receptor were prepared according to WO 2004/52092 and tested in comparison to wild-type mice in the von-Frey model. As demonstrated in Figure 4) KO-Mice not having the sigma (1) receptor (knock-out mice) are not susceptible anymore to the allodynia inducing effects of capsaicin independent of the dose given compared to wild-type mice (called wild-type mice). This is clearly demonstrating the truth of the role of sigma receptors in allodynia and strengthens the claim to the role of all compounds binding to the sigma-receptor in allodynia.

Example 5: Effects of BD-1063 in the von Frey model (mechanical allodynia) in mice exposed to the sciatic nerve injury

Surgery

The partial sciatic nerve ligation model was used to induce neuropathic pain (Malmberg and Basbaum, *Pain* 76: 215-222, 1998). This model consists of injury to the sciatic nerve at mid-to high level. Briefly, mice were anaesthetized with halothane (induction: 3%; surgery: 1%) and the common sciatic nerve was exposed at the level of the mid-thigh of the right paw. In control animals (sham-operated mice), an identical dissection was performed on the right paw except that the sciatic nerve was not ligated (Control). Nociceptive sensitivity was then measured was quantified by measuring the hind paw withdrawal response to von Frey filament stimulation as mentioned above. Animals underwent surgery on day 0; 11 days after surgery BD-1063 was injected subcutaneously in one group and the responses to mechanical stimuli were determined by means of the von Frey model in this and the none-treated group (before surgery) a reference value was measured in order to determine a baseline value.

filaments with 0.5 g being typically in the range of allodynia and 4 g clearly being in the general pain field.

Example 4: Effect of the von Frey-Model on KO mice.

KO mice lacking the sigma 1 receptor were prepared according to WO 2004/52092 and tested in comparison to wild-type mice in the von-Frey model. As demonstrated in Figure 4) KO-Mice not having the sigma (1) receptor (knock-out mice) are not susceptible anymore to the allodynia inducing effects of capsaicin independent of the dose given compared to wild-type mice (called wild-type mice). This is clearly demonstrating the truth of the role of sigma receptors in allodynia and strengthens the claim to the role of all compounds binding to the sigma-receptor in allodynia.

Example 5: Effects of BD-1063 in the von Frey model (mechanical allodynia) in mice exposed to the sciatic nerve injury

Surgery

The partial sciatic nerve ligation model was used to induce neuropathic pain (Malmberg and Basbaum, *Pain* 76: 215-222, 1998). This model consists of injury to the sciatic nerve at mid-to high level. Briefly, mice were anaesthetized with halothane (induction: 3%; surgery: 1%) and the common sciatic nerve was exposed at the level of the mid-thigh of the right paw. In control animals (sham-operated mice), an identical dissection was performed on the right paw except that the sciatic nerve was not ligated (Control). Nociceptive sensitivity was then measured was quantified by measuring the hind paw withdrawal response to von Frey filament stimulation as mentioned above. Animals underwent surgery on day 0; 11 days after surgery BD-1063 was injected subcutaneously in one group and the responses to mechanical stimuli were determined by means of the von Frey model in this and the none-treated group (before surgery) a reference value was measured in order to determine a baseline value.

Figures:

Figure 1) refers to example 1 and shows the test protocol for all tests with von Frey filaments.

Figure 2 a to c) refer to example 2 and show the effect of NE-100 a specific sigma receptor inhibtor (IC_{50} = 1.3 nM; J Med Chem 1999, 42(19): 3965) In a model of allodynia, especially mechanical allodynia.

Figure 2a) shows the dose dependency of the treatment with NE-100 to show analgesia in capsaicin-induced allodynia.

Figure 2b) demonstrates that the treatment with NE-100 is effective specifically in mechanical allodynia and not general pain as shown by the different efficacy depending on the force of the von-Frey filaments with 0.5 g being typically in the range of allodynia and 4 g clearly being in the general pain field. ***A:** Solvent, **B:** NE-100 [64 mg/Kg]*

Figure 2c) proofs that the effect of the treatment with NE-100 is clearly connected to its sigma inhibitor activity, as PRE-084 is a well known sigma receptor agonist.

Figures 3 a to d) refer to example 3 and shows the effect of antisense ODNs against sigma (1) receptor.

Figure 3a) shows the test protocol for Oligodesoxynucleotid (ODN) tests with von Frey filaments.

Figure 3b) shows the influence of the wash-out period on the effect t of treatment with antisense ODN, with two known antisense ODN (by King et al. (1997) Eur J Pharmacol 331:R5-R6 and Ueda et al. (2001) J.Pharmacol.Exp.Ther. 298, 703-710) being used proving their highly significant effect on allodynia in the von-Frey model. Still after 7 days washout the effect is gone as has to be expected from antisense ODN. Mismatches do not have any significant effect. ***A:** Saline 2 µl/mouse, **B:** ODN KING 10 µg/mouse, **C:** ODN UEDA 10 µg/mouse, **D:** Mismatch UEDA 10 µg/mouse*

Figure 3c) shows the effectiveness and dose dependency with two known antisense ODNs (by King et al. (1997) Eur J Pharmacol 331:R5-R6 and Ueda et al. (2001) J.Pharmacol.Exp.Ther. 298, 703-710) testing with von Frey filaments. Mismatches do not have any significant effect. ***A:*** *ODN UEDA,* ***B:*** *Mismatch UEDA,* ***C:*** *ODN KING,* ***D:*** *Mismatch KING*

Figure 3d) demonstrates that the treatment with two known antisense ODNs is effective specifically in mechanical allodynia and not general pain as shown by the different efficacy depending on the force of the von-Frey filaments with 0.5 g being typically in the range of allodynia and 4 g clearly being in the general pain field. ***A:*** *Saline 2 µl/mouse,* ***B:*** *ODN KING 10 µg/mouse,* ***C:*** *Mismatch KING 10 µg/mouse,* ***D:*** *ODN UEDA 10 µg/mouse,* ***E:*** *Mismatch UEDA 10 µg/mouse.*

Figure 4) refers to example 4 and demonstrates clearly that KO-Mice not having the sigma (1) receptor (called "mutantes") are not susceptible anymore to the allodynia-inducing effects of capsaicin independent of the dose given compared to wild-type mice. This is clearly demonstrating the truth of the role of sigma receptors in allodynia and strengthens the claim to the role of all compounds binding to the sigma-receptor in allodynia. ***A:*** *Wild-type mice,* ***B:*** *Knock-out mice.*

Figure 5) refers to example 5 and demonstrates the effects of BD-1063, a known antagonist (IC_{50}=30 nM sigma-1/800 nM sigma-2) in the von Frey model (mechanical allodynia) in mice exposed to the sciatic nerve injury. **A:** Baseline: Day 0, before surgery; **B:** Allodynic effects of sciatic nerve surgery on Day 11; **C:** Day 11 = BD-1063 (60mg/kg) subcutaneous administration. It can be clearly seen that BD-1063, being a specific sigma receptor antagonist, antagonizes mechanical allodynia in mice exposed to the (ipsilateral) sciatic nerve injury significantly. It can also be clearly demonstrated that the mechanical allodynia is attributed to the sigma-1 receptor since heterozygous mice only show half of the mechanical allodynic response. Knock-out mice do not develop mechanical allodynia.

Figure 6) refers to example 6 and demonstrates the Effects of BD-1063, a known antagonist, in the von Frey model (mechanical allodynia) in sham-operated mice. **A:** Day 0 = Baseline; before sciatic nerve surgery; **B:** Effects of sciatic nerve surgery; **C:** Administration of BD-1063 (60mg/kg) on Day 11. This control experiments clearly shows that the effect shown in Figure 5) is sigma-specific.

CLAIMS

1. Use of at least one compound binding to the sigma receptor for the production of a medicament for the treatment of mechanical allodynia.

2. Use, according to claim 1, characterized in that said compound may be in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.

3. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤5000 nM.

4. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤1000 nM.

5. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤500 nM.

6. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤250 nM.

7. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤100 nM.

8. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤50 nM.

9. Use, according to any of claims 1 to 8, characterized in that said compound binding to the sigma receptor used is acting on the sigma receptor as an antagonist.

10. Use, according to any of claims 1 to 8, characterized in that said compound binding to the sigma receptor used is acting on the sigma receptor as a partial antagonist.

11. Use, according to any of claims 1 to 8, characterized in that said compound binding to the sigma receptor used is acting on the sigma receptor as an inverse agonist.

12. Use, according to any of claims 1 to 11, characterized in that said compound binding to the sigma receptor is binding to the sigma-1 receptor subtype.

13. Use, according to claim 1, characterized in that said compound binding to the sigma receptor is selected from the group consisting of:

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)-Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-Yl]-Methanone	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)
1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-{[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl}-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2- Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-

Piperidin-2-Ylmethyl Ester	Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino]Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline
ARC 239 DiHCl	Astemizole
Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063
Benextramine TetraHCl	Benfluorex HCl
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepridil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DiHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl
Buclizine HCl	Buflomedil HCl
Bupropion HCl	Buspirone HCl

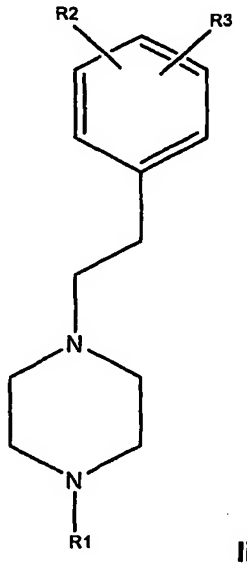
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 723C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DiHCl DiH2O
Carvedilol	Cephapirin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate
Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl
Clidinium Bromide	Clobenpropit 2HBr
Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphemanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl
Donepezil HCl	Doxepin HCl
Droperidol	Duloxetine
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Ethaverine HCl	Ethopropazine HCl
Eticlopride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl

GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate
Guanabenz Acetate	Guanadrel Sulfate
Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl
Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl
lomerizine diHCl	Loperamide HCl
Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl
N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-Piperazin-1-Yl}-Ethoxy)-Ethyl Ester
Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A

Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt
Perospirone	Perphenazine
Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenosafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino-Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Propericyazine	Propiomazine
Propranolol HCl	Protokylol
Protriptyline HCl	Pyrilamine Maleate
Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Rimantadine HCl
Risperidone	Ritanserin
Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296
Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Terconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate

Thioperamide Maleate	Thioproperazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-
Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Triprolidine HCl	Triprolidine HCl Z Isomer
Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

14. Use, according to claim 1, characterized in that said compound binding to the sigma receptor is of general formula IB



IB

wherein

R1 is selected from C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;
R2 and R3 are independently of each other selected from H; C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

in the production of a drug for the treatment of mechanical allodynia.

15. Use, according to claim 14, wherein R1 is selected from C_{1-6}-Alkyl, saturated or unsaturated, branched or not branched, unsubstituted or substituted with F, Cl, Br, I, NH_2, SH or OH.

16. Use, according to claim 14, wherein R2 and R3 are independently of each other selected from H; C_{1-6}-Alkyl, saturated or unsaturated, branched or not branched, unsubstituted or substituted with F, Cl, Br, I, NH_2, SH or OH; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, branched or not branched, unsubstituted or substituted with F, Cl, Br, I, NH_2, SH or OH.

17. Use, according to any of claims 14 to 16, characterized characterized in which for the compound according to general formula IB

R^1 is selected from C_{1-4}-Alkyl, saturated or unsaturated, substituted or not substituted, and branched or not branched;

preferably R^1 is selected from C_{1-4}-Alkyl, saturated, substituted or not substituted, and branched or not branched;

more preferably R^1 is selected from C_{1-4}-Alkyl, saturated, not substituted, and branched or not branched; namely CH_3, C_2H_5, C_3H_7, C_4H_9.

18. Use, according to any of claims 14 to 17, characterized in which for the compound according to general formula IB

R^2 and R^3 are independently of each other selected from H; OH, SH, NH_2, C_{1-4}Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; F, Cl, Br, I; O-C_{1-4}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

preferably R^2 and R^3 are independently of each other selected from H; OH, NH_2, C_{1-4}Alkyl, saturated, substituted or not substituted, and branched or not branched; F, Cl, Br, I; O-C_{1-4}-Alkyl, saturated, not substituted, and branched or not branched.

19. Use, according to any of claims 14 to 18, characterized in which for the compound according to general formula IB

R2 and R3 are independently of each other selected from H, OH, NH2, CH3, C2H5, C3H7, C4H9, CF3, CHF2, Cl, F, Br, I, O-CH3, O-C2H5, O-C3H7, O-C4H9;

preferably R2 and R3 are independently of each other selected from H, F, Cl and CF3

and/or are in 3' and 4' position respectively.

20. Use according to any of claim 1, wherein said compound is 1-(3,4-dichlorophenethyl)-4-methylpiperazine.

21. Use according to claim 1, wherein said compound is N1-(3,4-dichlorophenethyl)-N1,N2,N2-trimethylethane-1,2-diamine.

Fig. 1)

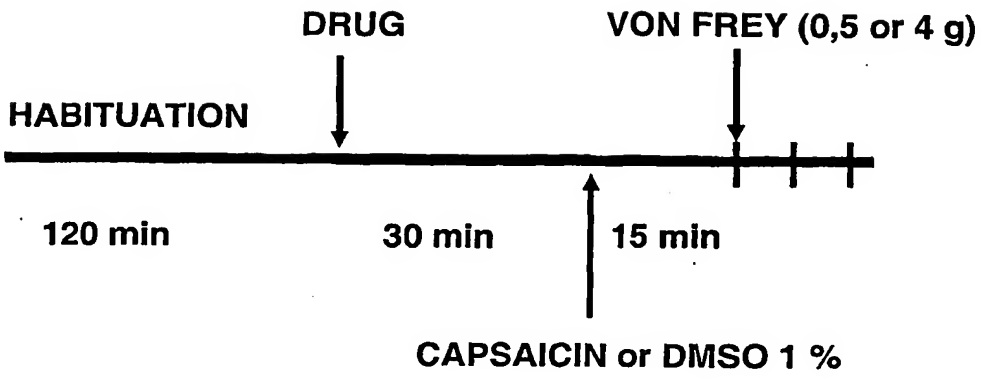

DRUG
VON FREY (0,5 or 4 g)
HABITUATION
120 min
30 min
15 min
CAPSAICIN or DMSO 1 %

Fig. 2a)

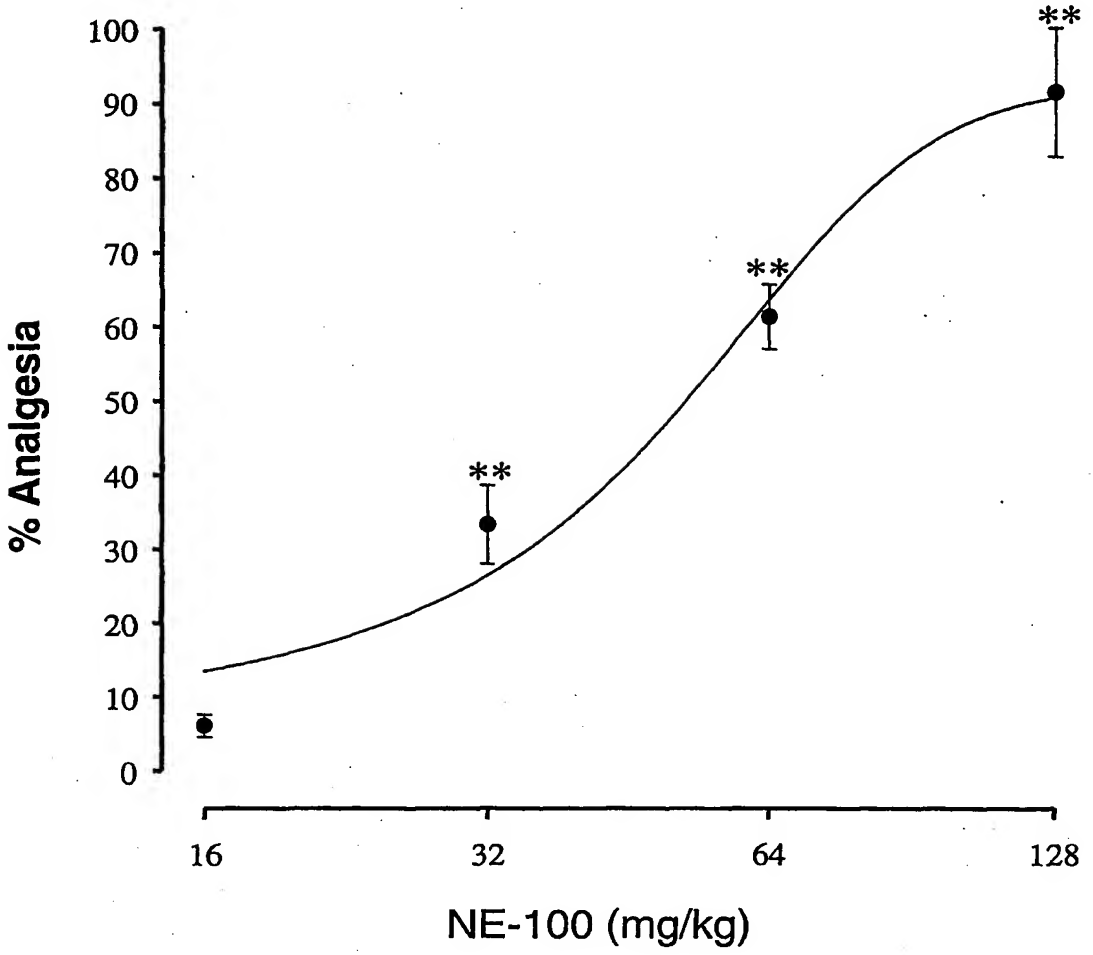


Fig. 2b)

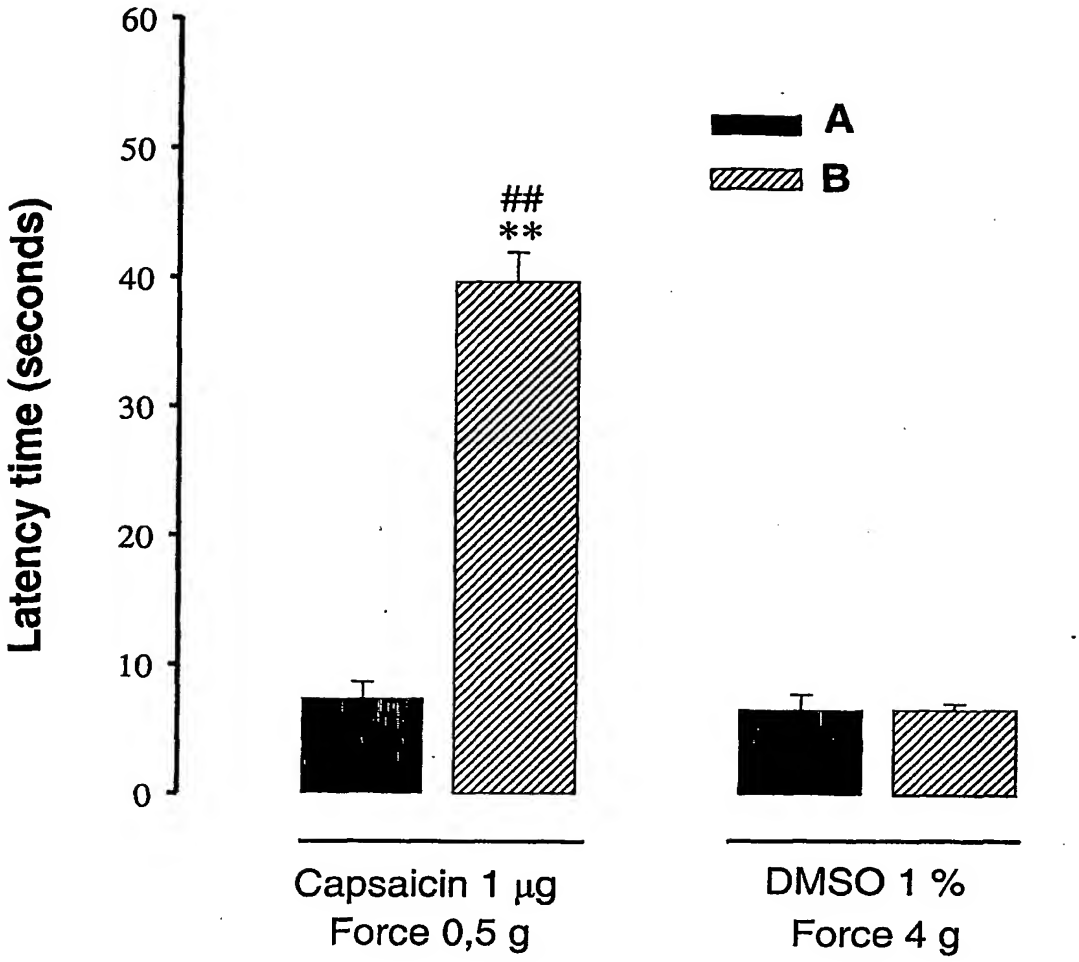

Latency time (seconds)
60
50
40
30
20
10
0
A
B
##
**
Capsaicin 1 µg
Force 0,5 g
DMSO 1 %
Force 4 g

Fig. 2c)

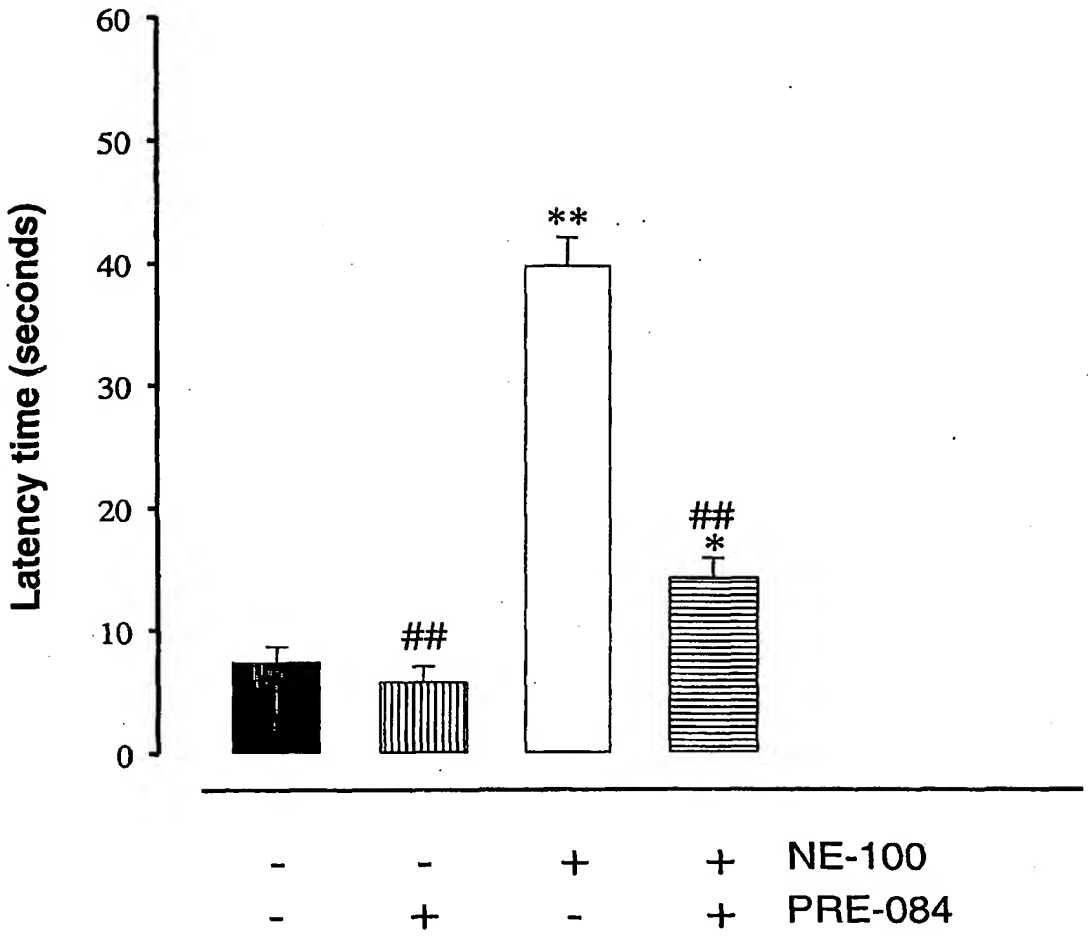


Fig. 3a)

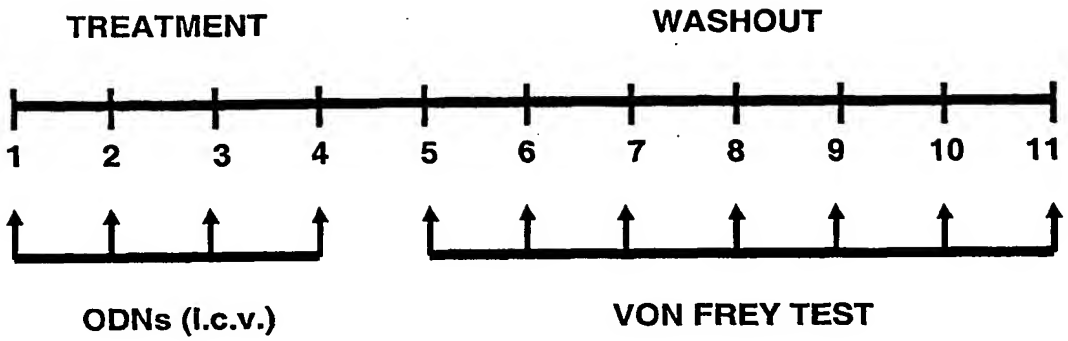


Fig. 3b)

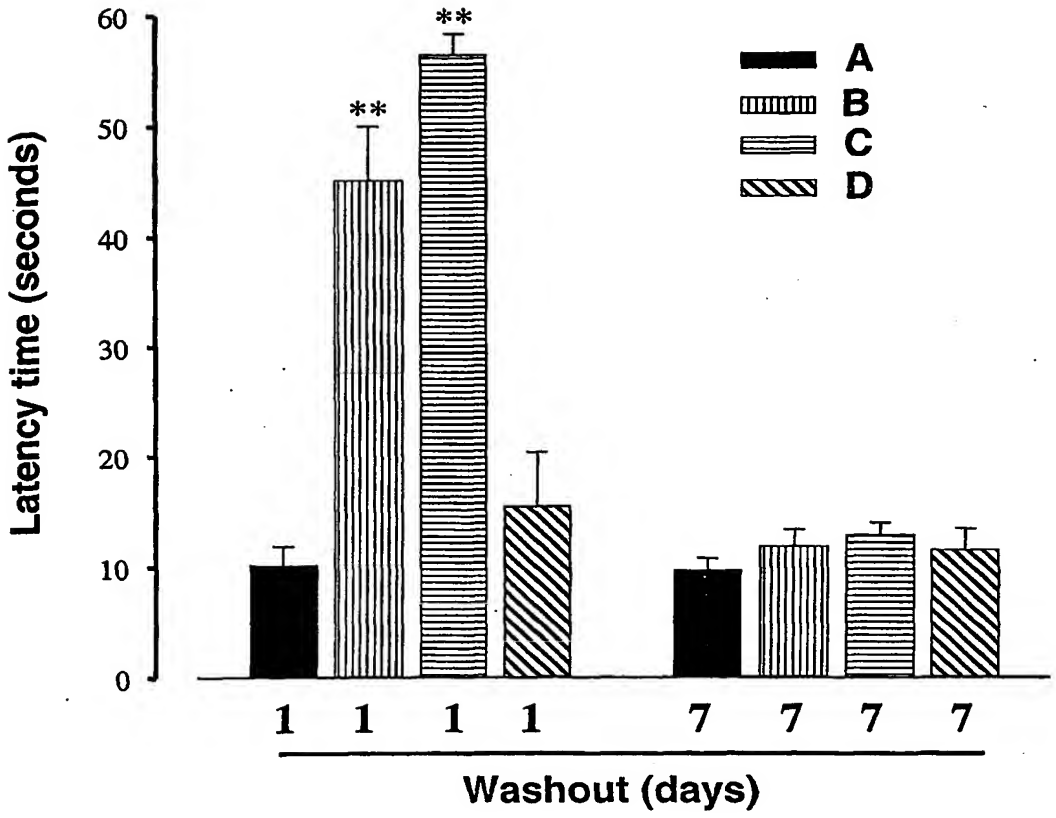


Fig. 3c)

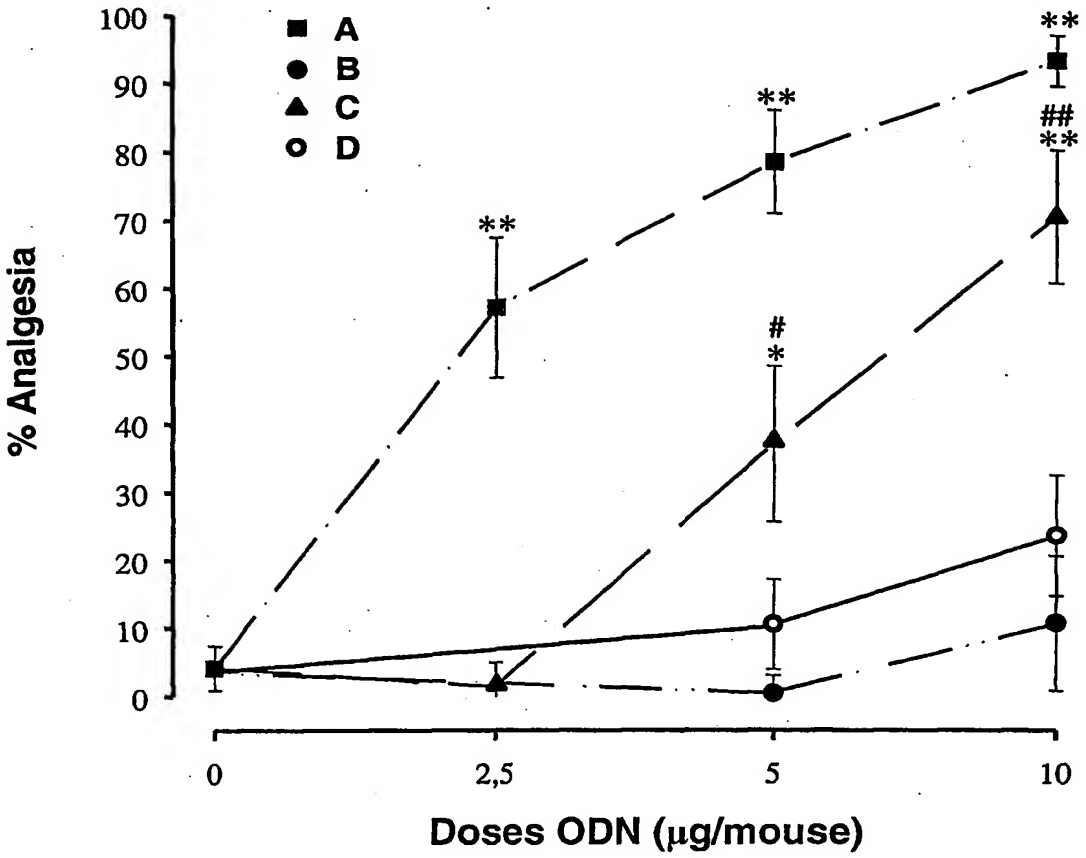

100
90
80
70
60
50
40
30
20
10
0
% Analgesia
A
B
C
D
**
**
**
##
#
*
0
2,5
5
10
Doses ODN (µg/mouse)

Fig. 3d)

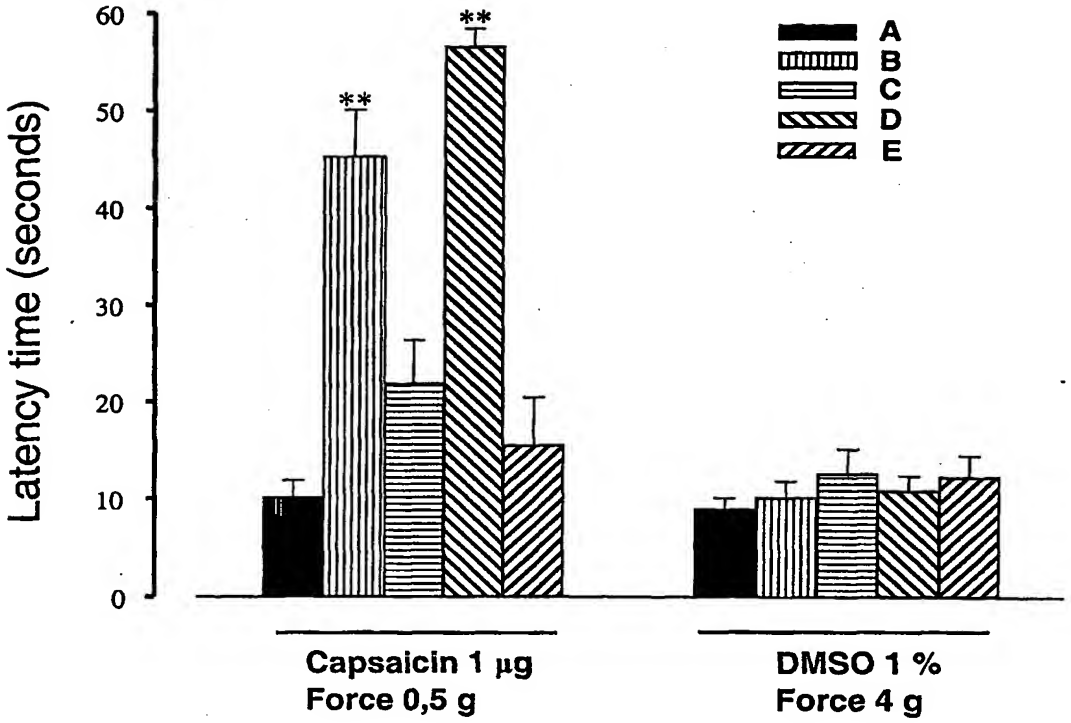


Fig. 4)

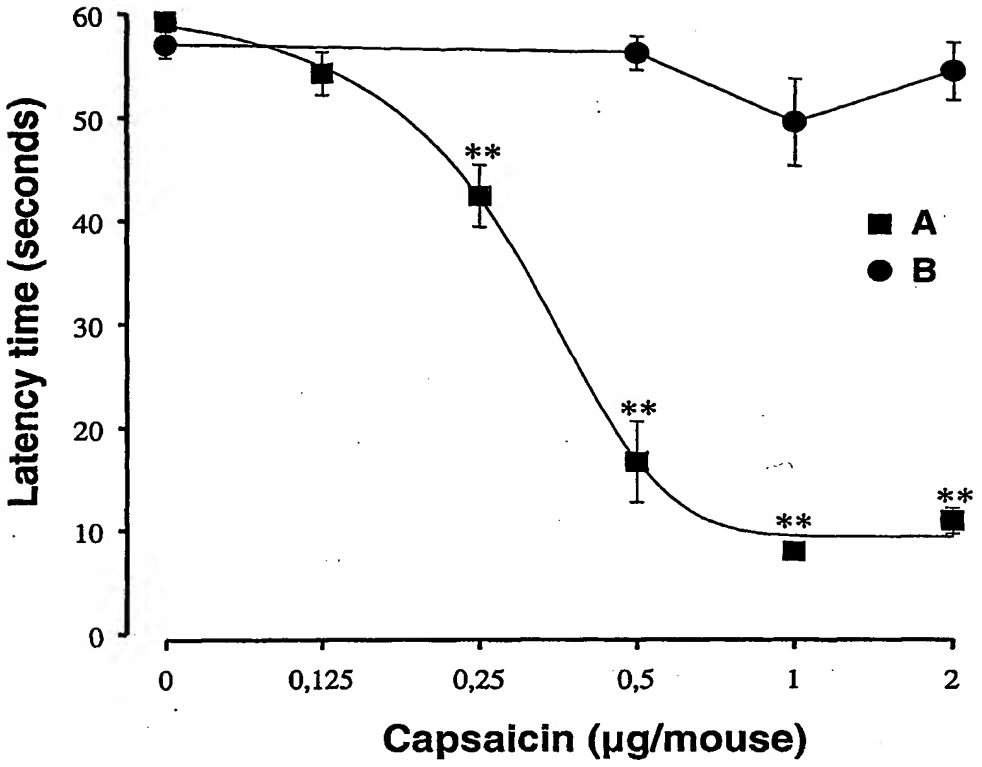

Latency time (seconds)
60
50
40
30
20
10
0
**
**
**
**
A
B
0
0,125
0,25
0,5
1
2
Capsaicin (µg/mouse)

Fig. 5)

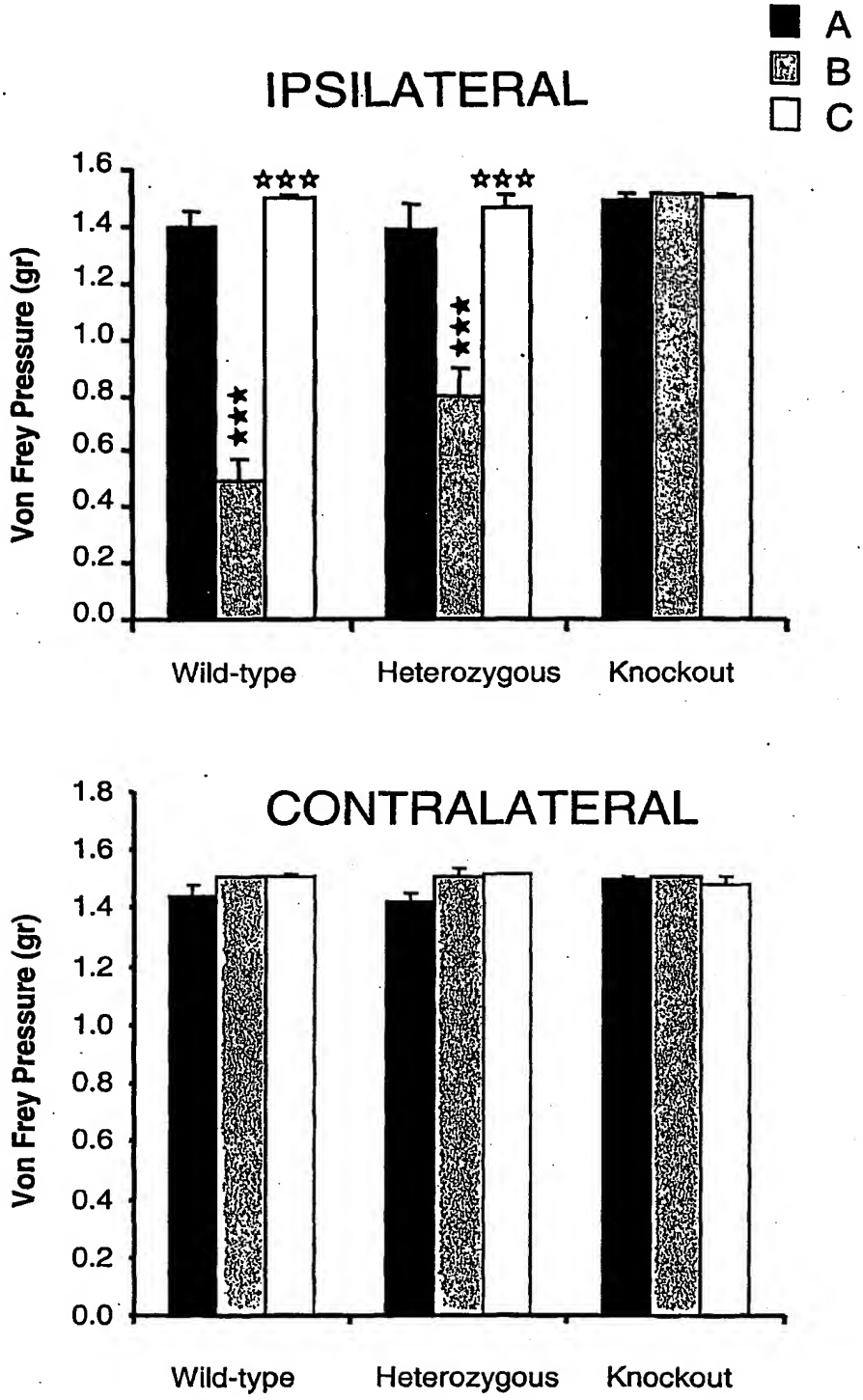
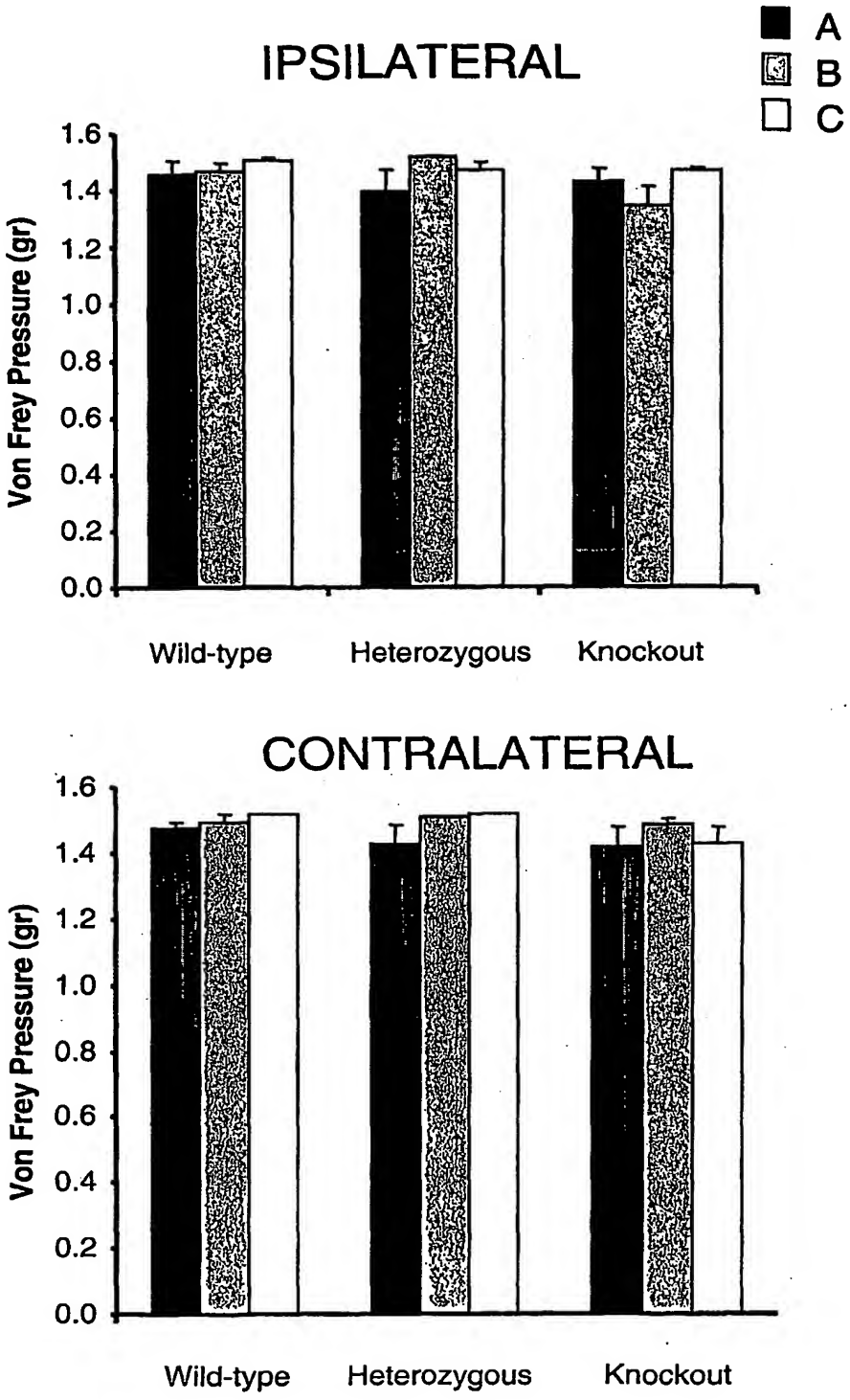


Fig. 6)



INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/EP2005/008080

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/13 A61P29/00 A61P25/00 A61K31/7125

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 596 756 B1 (GOLDSTEIN DAVID JOEL ET AL) 22 July 2003 (2003-07-22) column 10, lines 19-57	1-13
X	EP 1 244 498 B (WARNER-LAMBERT COMPANY) 6 August 2003 (2003-08-06) page 2, lines 13-15	1-13
X	SJOGREN, P. ET AL.: "Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists" PAIN, vol. 59, 1994, pages 313-316, XP002356374 paragraph 'CASEREPORT3!; table 1	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2005	16/12/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Venturini, F

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INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/EP2005/008080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEWART, L.S.A. & MARTIN, W.J.: "Influence of positive analgesics on development of neuropathic pain in rats" COMPARATIVE MEDICINE, vol. 53, no. 1, February 2003 (2003-02), pages 29-36, XP009057765 paragraph 'RESULTS!; figures 1-4	1-13
A	US 2003/171347 A1 (MATSUMOTO RAE R) 11 September 2003 (2003-09-11) the whole document	14-19
A	WO 03/078437 A (THE UNIVERSITY OF QUEENSLAND; SMITH, MAREE, THERESE; BROWN, LINDSAY; H) 25 September 2003 (2003-09-25) claims	1-13

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/EP2005/008080

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6596756 B1	22-07-2003	NONE	
EP 1244498 B	06-08-2003	EP 1244498 A2	02-10-2002
		SI 1244498 T1	29-02-2004
US 2003171347 A1	11-09-2003	NONE	
WO 03078437 A	25-09-2003	AU 2003209850 A1	29-09-2003
		CA 2479098 A1	25-09-2003
		EP 1495026 A1	12-01-2005
		JP 2005524676 T	18-08-2005